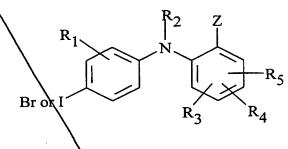
I

CLAIMS

What is claimed is:

- A method for treating or preventing arthritis in a mammal, said 1. method comprising the step of administering to a patient suffering from arthritis and in need of treatment, or to a patient suspected of developing arthritis, an effective antiarthritic amount of a MEK inhibitor.
- The method according to Claim 1 wherein the arthritis is 2. rheumatoid arthritis or osteoarthritis.
- The method according to Claim 2, wherein the arthritis is 3. osteoarthritis.
- The method according to Claim 2, wherein the arthritis is 4. rheumatoid arthritis.
- The method according to Claim\1, wherein said MEK inhibitor is a 5. selective MEK1 or MEK 2 inhibitor.
- The method according to Claim 1 wherein the MEK inhibitor is a compound of Formula I



wherein:

R₁ is hydrogen, hydroxy, C₁-C₈ alkyl, C₁-C₈ alkoxy, halo,

trifluoromethyl, or Ch

R₂ is hydrogen;

5

10

15

 R_3 , R_4 , and R_5 independently are hydrogen, hydroxy, halo, trifluoromethyl, C_1 - C_8 alkyl, C_1 - C_8 alkoxy, nitro, CN, or -(O or NH)_m-(CH₂)_n- R_9 , where R_9 is hydrogen, hydroxy, COOH, or NR₁₀R₁₁;

5

AZ

10

15

20

25

Part B, T

m is 0 or 1;

n is 0-4;

R₁₀ and R₁₁ independently are hydrogen or C₁-C₈ alkyl, or taken together with the nitrogen to which they are attached can complete a 3-10 member cyclic ring optionally containing 1, 2, or 3 additional heteroatoms selected from O, S, NH, or N-C₁-C₈ alkyl;

Z is COOR7, tetrazolyl, CONR₆R₇, CONHNR₁₀R₁₁, or CH₂OR₇; R₆ and R₇ independently are hydrogen, C₁-C₈ alkyl, C₂-C₈ alkenyl, C₂-C₈ alkynyl, (CO)-C₁-C₈ alkyl, aryl, heteroaryl, C₃-C₁₀ cycloalkyl, or C₃-C₁₀ (cycloalkyl optionally containing one, two, or three heteroatoms selected from O, S, NH, or N alkyl); or R₆ and R₇ together with the nitrogen to which they are attached complete a 3-10 member cyclic ring optionally containing 1, 2, or 3 additional heteroatoms selected from O, S, NH, or N alkyl; and wherein any of the foregoing alkyl, alkenyl, aryl, heterocyclic, and alkynyl groups can be unsubstituted or substituted by halo, hydroxy, C₁-C₆ alkoxy, amino, nitro, C₁-C₄ alkylamino, di(C₁-C₄)alkylamino, C₃-C₆ cycloalkyl, phenyl,phenoxy, C₃-C₅ heteroaryl, or C₃-C₅ heteroaryloxy; or a pharmaceutically acceptable salt, ester, amide, or prodrug thereof.

7. The method according to Claim 6 wherein the MEK inhibitor is a compound selected from:

[4-Chloro-2-(1H-tetrazol-5-yl)-phenyl-(4-iodo-2-methyl-phenyl)-amine;

(4-iodo-2-methyl-phenyl)-[2\((1H-tetrazol-5-yl)-phenyl)amine;

[4-nitro-2-(1H-tetrazdl-5-yl)-phenyl-(4-iodo-2-methyl-phenyl)amine; 4-Fluoro-2-(4-iodo-2-methylphenylamino)benzoic acid; 3,4,5-Trifluoro-2-(4-iodo-2-methyl-phenylamino)-benzoic acid; 5 3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-benzoic acid; 5-Bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-benzoic acid; 5-Chloro-2-(4-iodo-2-methyl-phenylamino)-benzoic acid; Sodium 5-Chloro-2-(4-iodd-2-methyl-phenylamino)-benzoate; 10 5-Bromo-2-(4-iodo-2-methyl-phenylamino)-benzoic acid; 2-(4-Iodo-2-methyl-phenylamino)-5-nitro-benzoic acid; 4-Chloro-2-(4-iodo-2-methyl-phenylamino)-benzoic acid; 2-(4-Iodo-2-methyl-phenylamino)-benzoic acid; 5-Fluoro-2-(4-iodo-2-methyl-phenylamino)-benzoic acid; 5-Iodo-2-(4-iodo-2-methyl-phenylamino)-benzoic acid; 2,3,5-Trifluoro-4-(4-iodo-2-methyl-phenylamino)-benzoic acid; 2-(4-Iodo-phenylamino)-5-methoxy-benzoic acid; 5-Methyl-2-(4-iodo-2-methyl-phenylamino)-benzoic acid; 2-(4-Iodo-2-methyl-phenylamino)-4-nitro-benzoic acid; 20 2-(4-Bromo-2-methyl-phenylamino)-4-fluoro-benzoic acid; 2-(2-Bromo-4-iodo-phenylamino)-5-nitro-benzoic acid; 2-(4-Bromo-2-methyl-phenylamino)-3,4-difluoro-benzoic acid; 5-Chloro-N-(2-hydroxyethyl)-2-(4-iodo-2-methyl-phenylamino)benzamide; 25 4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide; 4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-methyl-benzamide; N-Ethyl-4-fluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide; 4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N,N-dimethylbenzamide; 30 4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-(1H-tetrazol-5-yl)benzamide;

5-Bromo-2-(4-iodo-2-methyl-phenylarhino)-benzamide;

5-Chloro-2-(4-iodd-2-methyl-phenylamino)-N,N-dimethyl-
benzamide;
[5-Chloro-2-(4-iodo-2-methyl-phenylamino)-benzoylamino]-acetic
acid;
4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-propyl-benzamide;
5-Bromo-N-(2-hydroxy-ethyl)-2-(4-iodo-2-methyl-phenylamino)-
benzamide;
N,N-Diethyl-4-fluoro-2 (4-iodo-2-methyl-phenylamino)-
benzamide;
4-Fluoro-N-{3-[4-(2-hydroxy-ethyl)-piperazin-1-yl]-propyl}-
2-(4-iodo-2-methyl-phenylamino)-benzamide;
N,N-Diethyl-2-(4-iodo-2-methyl-phenylamino)-5-nitro-benzamide
N-Butyl-4-fluoro-2-(4-iodd-2-methyl-phenylamino)-benzamide;
5-Chloro-N,N-diethyl-2-(4-jodo-2-methyl-phenylamino)-
benzamide;
5-Bromo-2-(4-iodo-2-methyl-phenylamino)-N,N-dimethyl-
benzamide;
5-Bromo-3,4-difluoro-N-(2-hydroxy-ethyl)-2-(4-iodo-2-methyl-
phenylamino)-benzamide;
N-(2,3-Dihydroxy-propyl)-3,4-difluoro-2-(4-iodo-2-methyl-
phenylamino)-benzamide;
5-Bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-N-
(2-piperidin-1-yl-ethyl)-benzamide;
3,4-Difluoro-N-(2-hydroxy-ethyl)-2-(4-iodo-2-methyl-
phenylamino)-benzamide;
N-(2,3-Dihydroxy-propyl)-4-fluoro-2-(4-iodo-2-methyl-
phenylamino)-benzamide;
3,4-Difluoro-N-(3-hydroxy-propyl)-2-(4-iodo-2-methyl-
phenylamino)-benzamide;
5-Bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-N-
(2-pyrrolidin-1-yl-ethyl)-benzamide;
5-Bromo-3,4-difluoro-2-(4-iodo-2-methy)-phenylamino)-N-
(2-pyridin-4-yl-ethyl)-benzamide;

- 4-Fluoro-N-(2-hydroxy-ethyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide;
- 5-Bromo-N-(3-dimethylamino-propyl)-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide;
- 5-Bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-morpholin-4-yl-ethyl)-benzamide;
- 3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-morpholin-4-yl-ethyl)-benzamide;
- 3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-pyrrolidin-1-yl-ethyl)-benzamide;
- 3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-pyridin-4-yl-ethyl)-benzamide;
- N-(3-Dimethylamino-propyl)-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide;
 - N-Benzyl-4-fluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide;
- 2-(4-Bromo-2-methyl-phenylamino)-3,4-difluoro-N-(2-hydroxy-ethyl)-benzamide;
- 4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-morpholin-4-ylethyl)-benzamide;
- 4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-(3-piperidin-1-yl-propyl)-benzamide;
- 3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(3-piperidin-1-yl-propyl)-benzamide;
- 4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-thiophen-2-yl-ethyl)-benzamide;
- 4-Fluoro-2-(4-iodo-2-methyl-pherlylamino)-N-(2-pyrrolidin-1-yl-ethyl)-benzamide;
- 2-(4-Bromo-2-methyl-phenylamino)-3,4-difluoro-N-(2-morpholin-4-yl-ethyl)-benzamide;
- 5-Bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-N-pyridin-4-ylmethyl-benzamide;
- 3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-N-pyridin-4-ylmethyl-benzamide;

5

10

25

- 5-Chloro-2-(4-iodo 2-methyl-phenylamino)-N-(2-piperidin-1-yl-ethyl)-benzamide;
- (3-Hydroxy-pyrrolidin-1-yl)-[2-(4-iodo-2-methyl-phenylamino)-5-nitro-phenyl]-methanone;
- 5-Chloro-2-(4-iodo-2-methyl-phenylamino)-N-(2-pyrrolidin-1-yl-ethyl)-benzamide;
- 5-Bromo-N-(2-diethylamino-ethyl)-2-(4-iodo-2-methyl-phenylamino)- benzamide;
- N-{2-[Bis-(2-hydroxy-ethyl)-amino]-ethyl}-5-chloro-2-(4-iodo-2-methyl-phenylamino)- benzamide;
- N-{2-[Bis-(2-hydroxy-ethyl)-amino]-ethyl}-5-bromo-2-(4-iodo-2-methyl-phenylamino)- benzamide
- N-{3-[4-(2-Hydroxy-ethyl)-piperazin-1-yl]-propyl}-2-(4-iodo-2-methyl-phenylamino)- benzamide;
- 5-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-pyridin-4-ylmethylbenzamide;
- 5-Bromo-2-(4-iodo-2-ethyl-phenylamino)-N-(2-pyrrolidin-1-yl-ethyl)-benzamide;
- 5-Bromo-2-(4-iodo-2-methyl-phenylamino)-N-(2-piperidin-1-yl-ethyl)-benzamide;
- 5-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-pyrrolidin-1-yl-ethyl)-benzamide;
- 5-Chloro-N-(3-dimethylamino-propyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide;
- N-{2-[Bis-(2-hydroxy-ethyl)-amino]-ethyl}-5-fluoro-2-(4-iodo-2-methyl-phenylamino)- benzamide;
- 5-Chloro-N-(3-hydroxy-propyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide;
- 5-Chloro-N-(3-diethylamino-2-hydroxy-propyl)-2-(4-iodo-2-methyl-phenylamino)- benzamide;
- 5-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-piperidin-1-yl-ethyl)-benzamide;

20

25

10

20

25

- 5-Bromo-N-(3-hydroxy-propyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide;
- 5-Bromo-2-(4-iodo-2-methyl-phenylamino)-N-(3-piperidin-1-yl-propyl)-benzamide;
- N-{2-[Bis-(2-hydroxy-ethyl)-amino]-ethyl}-2-(4-iodo-2-methyl-phenylamino)-5-nitro- benzamide;
- 5-Chloro-2-(4-iodo-2-methyl-phenylamino)-N-(2-morpholin-4-yl-ethyl)-benzamide;
- 5-Chloro-N-(3-diethylamino-propyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide;
- 5-Chloro-N-(2-diisopropylamino-ethyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide;
- 5-Chloro-2-(4-iodo-2-methyl-phenylamino)-N-(3-piperidin-1-yl-propyl)-benzamide;
- 2-(4-Iodo-2-methyl-phenylamino)-5-nitro-N-(2-piperidin-1-yl-ethyl)-benzamide;
- 5-Bromo-2-(4-iodo-2-methyl-phenylamino)-N-(2-piperazin-1-yl-ethyl)-benzamide;
- N-(2-Diethylamino-ethyl)-5-fluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide;
- 5-Bromo-N-(3-dimethylamino-propyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide;
- N-(3-Hydroxy-propyl)-2-(4-iodo-2-methyl-phenylamino)-5-nitrobenzamide;
- 5-Fluoro-N-(3-hydroxy-propyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide;
- N-(3-Diethylamino-propyl)-5-fluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide;
- N-(3-Diethylamino-propyl)-2-(4-iodo 2-methyl-phenylamino)-5-nitro-benzamide;
- 5-Bromo-2-(4-iodo-2-methyl-phenylamino)-N-(2-morpholin-4-yl-ethyl)-benzamide;

10 The transfer of the transfer o 20

5

2-(4-Iodo-2-methyl-phenylamino)-5-nitro-N-(3-piperidin-1-ylpropyl)-benzamide; [5-Fluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-(3-hydroxypyrrolidin-1-yl)-methanone 5-Bromo-N-(2-diisopropylamino-ethyl)-2-(4-iodo-2-methylphenylamino)-benzamide; 5-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-morpholin-4-ylethyl)-benzamide; 5-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-(3-piperidin-1-ylpropyl)-benzamide; [5-Fluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-[4-(2-hydroxy-ethyl)-piperazin-1-yl]-methanone; N-(3-Diethylamino-2-hydroxy-propyl)-5-fluoro-2-(4-iodo-2-methyl-phenylamino)- benzamide; N-Cyclopropyl-5-fluoro-2-(4-iodo-2-methyl-phenylamino)benzamide; 5-Chloro-N-(2-hydroxy-ethyl)-2-(4-iodo-2-methyl-phenylamino)benzamide; 5-Fluoro-N-(2-hydroxy-ethyl)-2-(4-iodo-2-methyl-phenylamino)benzamide; N-Benzyloxy-5-fluoro-2-(4-iodo-2-methyl-phenylamino)benzamide; N-Benzyloxy-5-bromo-2-(4-iodo-2-methyl-phenylamino)benzamide; benzamide;

25

30

2-(4-Iodo-2-methyl-phenylamino) \sqrt{5-nitro-N-(4-sulfamoyl-benzyl)-

5-Bromo-N-(2-hydroxy-ethyl)-2-(4-liodo-2-methyl-phenylamino)benzamide:

N-(2-Hydroxy-ethyl)-5-iodo-2-(4-iodo-2-methyl-phenylamino)benzamide;

N-(2-Hydroxy-ethyl)-2-(4-iodo-2-ethyl-phenylamino)-5-nitrobenzamide;

benzamide; 5-Chloro-N-cyclopr\(\text{pyl-2-(4-iodo-2-methyl-phenylamino)-} \) benzamide; 5 5-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-methyl-N-phenylbenzamide; N-Allyl-5-fluoro-2-(4-iddo-2-methyl-phenylamino)-benzamide; N-Benzyloxy-5-iodo-2-(\frac{1}{4}-iodo-2-methyl-phenylamino)benzamide; 10 5-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-(4-sulfamoylbenzyl)-benzamide; N-Allyl-5-chloro-2-(4-iodd-2-methyl-phenylamino)-benzamide; N-Cyclopropyl-2-(4-iodo-2-methyl-phenylamino)-5-nitro-benzamide; 5-Bromo-N-cyclopropyl-2-(\frac{1}{4}-iodo-2-methyl-phenylamino)benzamide; 5-Chloro-2-(4-iodo-2-methyl-phenylamino)-N-methyl-N-phenylbenzamide; 5-Iodo-2-(4-iodo-2-methyl-phenylamino)-N-(4-sulfamoyl-benzyl)benzamide; 20 5-Bromo-2-(4-iodo-2-methyl-phenylamino)-N-(4-sulfamoylbenzyl)-benzamide; N-Allyl-2-(4-iodo-2-methyl-phenylamino)-5-nitro-benzamide; 2-(4-Iodo-2-methyl-phenylamino)-5-nitro-N-(4-sulfamoyl-benzyl)-25 benzamide; N-Allyl-5-bromo-2-(4-iodo-2-methyl-phenylamino)-benzamide; 5-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-(3-methyl-benzyl)benzamide; N-Cyclopropyl-5-iodo-2-(4-iodo-2-methyl-phenylamino)benzamide; 30

benzamide;

5-Bromo-2-(4-iodo-2-methyl-phenylamino)-N-methyl-N-phenyl-

2-(4-Iodo-2-methyl-phenylamino)-N-methyl-5-nitro-N-phenyl-

25

30

N-Benzyloxy-2-(4-iodo-2-methyl-phenylamino)-5-nitrobenzamide: N-Cyclohexyl-5-iodo-2-(4-iodo-2-methyl-phenylamino)benzamide; N-Allyl-5-iodo-2-(4-lodo-2-methyl-phenylamino)-benzamide; 5-Iodo-2-(4-iodo-2-methyl-phenylamino)-N-(3-methyl-benzyl)benzamide; 2-(4-Iodo-2-methyl-phenylamino)-N-(3-methyl-benzyl)-5-nitrobenzamide; 5-Iodo-2-(4-iodo-2-methyl-phenylamino)-N-methyl-N-phenylbenzamide; N-Cyclohexyl-5-fluoro-2-(4-iodo-2-methyl-phenylamino)benzamide; 5-Chloro-N-cyclohexyl-2-(4-iodo-2-methyl-phenylamino)benzamide; 5-Bromo-2-(4-iodo-2-methyl-phenylamino)-N-(3-methyl-benzyl)benzamide; 5-Bromo-N-cyclohexyl-2-(4-iodo-2-methyl-phenylamino)benzamide; 5-Chloro-2-(4-iodo-2-methyl\phenylamino)-N-(3-methyl-benzyl)benzamide; N-Cyclohexyl-2-(4-iodo-2-methyl-phenylamino)-5-nitrobenzamide; N-Benzyloxy-5-bromo-2-(4-iodb-2-methyl-phenylamino)benzamide; N-Benzyloxy-5-fluoro-2-(4-iodo-2-methyl-phenylamino)benzamide: 5-Chloro-N-(2-hydroxy-ethyl)-2-(4-iodo-2-methyl-phenylamino)benzamide: 5-Bromo-N-(2-hydroxy-ethyl)-2-(4-iodo-2-methyl-phenylamino)benzamide; 2-(4-Iodo-2-methyl-phenylamino)-N-methyl-5-nitro-N-phenylbenzamide;

WO 00/35436

PCT/US99/29783

5-Chloro-2-(4-iodo-2-methyl-phenylamino)-N-methyl-N-phenylbenzamide; N-(2-Hydroxy-ethyl)-\$-iodo-2-(4-iodo-2-methyl-phenylamino)benzamide; 5-Chloro-N-cyclopropyl-2-(4-iodo-2-methyl-phenylamino)-5 benzamide; N-Allyl-5-chloro-2-(4-iodo-2-methyl-phenylamino)-benzamide; 5-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-methyl-N-phenylbenzamide; 10 N-(2-Hydroxy-ethyl)-2-(4-jodo-2-methyl-phenylamino)-5-nitrobenzamide; 5-Fluoro-N-(2-hydroxy-ethyl)-2-(4-iodo-2-methyl-phenylamino)benzamide; 5-Bromo-N-cyclopropyl-2-(4-iodo-2-methyl-phenylamino)benzamide; N-Cyclopropyl-5-fluoro-2-(4-lodo-2-methyl-phenylamino)benzamide; 5-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-(4-sulfamoylbenzyl)-benzamide; N-Cyclopropyl-2-(4-iodo-2-methyl-phenylamino)-5-nitro-20 benzamide; N-Allyl-5-fluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide; N-Benzyloxy-5-iodo-2-(4-iodo-2-methyl-phenylamino)benzamide; 25 N-Allyl-5-bromo-2-(4-iodo-2-methyl-phenylamino)-benzamide; 5-Bromo-2-(4-iodo-2-methyl-phenylamino)-N-(4-sulfamoylbenzyl)-benzamide; 5-Bromo-2-(4-iodo-2-methyl-phenylamino)-N-methyl-N-phenylbenzamide: 30 N-Allyl-2-(4-iodo-2-methyl-phenylamino)-5-nitro-benzamide; 4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-benzyl alcohol; [5-Chloro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-methanol;

[2-(4-Iodo-2-methyl-phenylamino)-5-nitro-phenyl]-methanol;

WO 00/35436

PCT/US99/29783

Jul B1

10

(O

<u>15</u>

ſΨ

O

[5-Bromo-2-(4-iodo-2-methyl-phenylamino)-phenyl]-methanol;

and

N-Allyl-2-(4-iodo-2-methyl-phenylamino)-5-nitro-benzamide.

5 A3

The method of claim 6, wherein the MEK inhibitor is a compound of Formula (I) wherein (a) R₁ is hydrogen, methyl, methoxy, fluoro, chloro, or bromo; (b) R2 is hydrogen; (c) R3, R4, and R5 independently are hydrogen, fluoro, chloro, bromo, iodo, methyl, methoxy, or nitro; (d) R_{10} and R₁₁ independently are hydrogen or methyl; (e) Z is COOR₇, tetrazolyl, $CONR_6R_7$, $CONHNR_{10}R_{11}$, or CH_2OR_7 ; R_6 and R_7 independently are hydrogen, C 1-4 alkyl heteroaryl, or C 3-5 cycloalkyl optionally containing one or two heteroatoms selected from O, S, or NH; or R₆ and R₇ together with the nitrogen to which they are attached complete a 5-6 member cyclic ring optionally containing Nor 2 additional heteroatoms selected from O, NH or N-alkyl; and wherein any of the foregoing alkyl or aryl groups can be unsubstituted or substituted by halo, hydroxy, methoxy, ethoxy, or heteroaryloxy; (f) Z is COOR₇;\(g) R7 is H, pentafluorophenyl, or tetrazolyl; (h) R_3 , R_4 , and R_5 are independently H, fluoro, or chloro; (i) R_4 is fluoro; (j) two of R3, R4, and R5 are fluoro; or (k) or combinations of the above.

but by Cont

- 9. The method of claim 8, wherein the MEK inhibitor is a compound of Formula (I) wherein: Z is COOR; R_7 is H, pentafluorophenyl, or tetrazolyl; R_3 and R_5 are independently H, fluoro, or chloro; and R_4 is fluoro.
- 10. The method of Claim 1 wherein the MEK inhibitor is a compound of Formula II

II

wherein:

R_{1a} is hydrogen, hydroxy, C₁-C₈ alkyl, C₁-C₈ alkoxy, halo, trifluoromethyl, or QN;

R_{2a} is hydrogen;

 R_{3a} , R_{4a} , and R_{5a} independently are hydrogen, hydroxy, halo, trifluoromethyl, C_1 - C_8 alkyl, C_1 - C_8 alkoxy, nitro, CN, or $(O \text{ or NH})_m$ - $(CH_2)_n$ - R_{9a} , where R_{9a} is hydrogen, hydroxy, CO_2H or $NR_{10a}R_{11a}$.

n is 0-4;

m is 0 or 1;

R_{10a} and R_{11a} independently are hydrogen or C₁-C₈ alkyl, or taken together with the nitrogen to which they are attached can complete a 3- to 10-member cyclic ring optionally containing one, two, or three additional heteroatoms selected from O, S, NH, or N-C₁-C₈ alkyl;

R_{6a} is hydrogen, C₁-C₈ alkyl, (CO)-C₁-C₈ alkyl, aryl, aralkyl, or C₃-C₁₀ cycloalkyl;

R_{7a} is hydrogen, C₁-C₈ alkyl, C₂-C₈ alkenyl, C₂-C₈ alkynyl,
C₃-C₁₀ (cycloalkyl or cycloalkyl optionally containing a heteroatom selected from O, S, or NR_{9a});

and wherein any of the foregoing alkyl, alkenyl, aryl, heteroaryl, heterocyclic, and alkynyl groups can be unsubstituted or substituted by halo, hydroxy, C₁-C₆ alkoxy, amino, nitro, C₁-C₄ alkylamino, di(C₁-C₄)alkylamino, C₃-C₆ cycloalkyl, phenyl, phenoxy, C₃-C₅ heteroaryl or

5

20

15

WO 00/35436 PCT/US99/29783

> heterocyclic radical, or C₃+C₅ heteroaryloxy or heterocyclic radical-oxy; or R_{6a} and R_{7a} taken together with the N to which they are attached can complete a 5- to 10-membered cyclic ring, optionally containing one, two, or three additional heteroatoms selected from O, S, or NR_{10a}R_{11a}; or a pharmaceutically acceptable salt, ester, amide or prodrug thereof.

10

5



- The method of Claim 10, comprising a MEK inhibitor having a 11. structure of Formula (II) wherein: (a) R_{1a} is H, methyl, fluoro, or chloro; (b) R_{2a} is H; R_{3a} , R_{4a} , and R_{5a} are each H, Cl, nitro, or F; (c) R_{6a} is H; (d) R_{7a} is methyl, ethyl, 2-propenyl, propyl, butyl, pentyl, hexyl, cyclopropylmethyl, cyclobutyl methyl, cyclopropylmethyl, or cyclopropylethyl; and (e) the 4' position is I, rather than Br.
- The method of claim 11\ comprising a MEK inhibitor having a 12. structure of Formula (II) wherein: R_{4a} is F at the 4 position, para to the CO-N-R_{6a}-OR_{7a} group and metal to the bridging nitrogen; at least one of R_{3a} and R_{5a} is F or Cl; and R_{1a} is methyl or chloro.
- The method of Claim 10, comprising a MEK inhibitor having a 13. formula selected from:
 - 4-Fluoro-N-hydroxy-2-(4-todo-2-methyl-phenylamino)-benzamide;
- 4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-(methoxy)benzamide;
- 4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-(prop-2-ynyloxy)benzamide;
- 4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-phenoxyethoxy)benzamide;
- 4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-thienylmethoxy)benzamide;
- 4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-(prop-2-enyloxy)benzamide;

4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-(cyclopropylmethoxy)-benzamide; 4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-(cyclopentoxy)-

benzamide;

3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-N(3-furylmethoxy)-benzamide;

3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-N-ethoxy-benzamide;

3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(but-2-enyloxy)-benzamide;

3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(cyclopropyl-methoxy)-benzamide;

3,4-Difluoro-2-(4-iodo-2 methyl-phenylamino)-N-(1-methylprop-2-ynyloxy)-benzamide;

3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(3-phenylprop-2-ynyloxy)-benzamide;

3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(3-methyl-5-phenylpent-2-en-4-ynyloxy)-benzamide;

3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(prop-2-ynyloxy)-benzamide;

3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(propoxy)-benzamide;

3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(cyclobutyloxy)-benzamide;

3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-thienylmethoxy)-benzamide;

3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-methyl-prop-2-enyloxy)-benzamide;

3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-phenoxyethoxy)-benzamide;

3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(but-2-enyloxy)-benzamide;

25

30

5

3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(but-3-ynyloxy)benzamide; 3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(cyclopentyloxy)-benzamide; 3,4-Difluoro-2-(4\iodo-2-methyl-phenylamino)-N-(3-(2-fluorophenyl)-prop-2-ynyloxy)-benzamide; 5-Bromo-3,4-difludro-N-hydroxy-2-(4-iodo-2-methylphenylamino)-benzamide; 5-Bromo-3,4-difluor\(\phi\)-2-(4-iodo-2-methyl-phenylamino)-N-(n-propoxy)-benzamide; 5-Bromo-3,4-difluord-N-(furan-3-ylmethoxy)-2-(4-iodo-2-methylphenylamino)-benzamide; 5-Bromo-N-(but-2-enyloxy)-3,4-difluoro-2-(4-iodo-2-methylphenylamino)-benzamide 5-Bromo-N-butoxy-3,4-difluoro-2-(4-iodo-2-methylphenylamino)-benzamide; 5-Bromo-3,4-difluoro-2\(4-iodo-2-methyl-phenylamino)-N-(3-methyl-but-2-enyloxy)-benzamide; 5-Bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(3-methyl-pent-2-en-4-ynyloxy)-benzamide; 5-Bromo-3,4-difluoro-2-(4-iodo-2-methyl-benzyl)-N-[5-(3-methoxy-phenyl)-3-methyl-pent-2-en-4-ynyloxy]-benzamide; 5-Bromo-3,4-difluoro-2-(4-lodo-2-methyl-phenylamino)-N-(prop-2-ynyloxy)-benzamide; 5-Bromo-3,4-difluoro-2-(4-io/do-2-methyl-phenylamino)-N-[3-(3-methoxy-phenyl)-prop-2-ynyloxy]-benzamide; 5-Bromo-3,4-difluoro-2-(4-iodp-2-methyl-phenylamino)-N-(thiopen-2-ylmethoxy)-benzamide; 5-Bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(pyridin-3-ylmethoxy)-benzamide; 5-Bromo-3-4-difluoro-2-(4-iodo-2-methyl-phenylamino)-N-

(3-(2-fluorophenyl)-prop-2-ynyloxy)-benzamide;

(ethoxy)-benzamide; 5-Bromo-3,4-difludro-2-(4-iodo-2-methyl-phenylamino)-N-(cyclopropylmethoxy)-benzamide; 5 5-Bromo-3,4-difluor \(\phi - 2 - (4-iodo-2-methyl-phenylamino \) - N-(isopropoxy)-benzamide; 5-Bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-N-but-3-ynyloxy)-benzamide; 5-Chloro-N-hydroxy-2\(4-iodo-2-methyl-phenylamino)-10 benzamide; 5-Chloro-2-(4-iodo-2-methyl-phenylamino)-N-(tetrahydro-pyran-2-yloxy)-benzamide; 5-Chloro-2-(4-iodo-2-methyl-phenylamino)-N-methoxybenzamide; 4-Bromo-2-(4-iodo-2-methyl-phenylamino)-N-phenylmethoxybenzamide; 4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-phenylmethoxybenzamide; 5-Fluoro-N-hydroxy-2-(4-iddo-2-methyl-phenylamino)-benzamide; 20 5-Iodo-2-(4-iodo-2-methyl-phenylamino)-N-phenylmethoxybenzamide; 5-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-(tetrahydropyran-2-yloxy)-benzamide; 3,4-Difluoro-2-(4-bromo-2-methyl-phenylamino)-N-25 (3-phenylprop-2-ynyloxy)-benzamide; 3,4-Difluoro-2-(4-bromo-2-methyl-phenylamino)-N-(3-furylmethoxy)-benzamide; 3,4-Difluoro-2-(4-bromo-2-methyl-phenylamino)-N-(2-thienylmethoxy)-benzamide; 30 3,4-Difluoro-2-(4-bromo-2-methyl-phenylamino)-N-(but-3-ynyloxy)-benzamide; 3,4-Difluoro-2-(4-bromo-2-methyl-phenylamino)-N-(2-methyl-

5-Bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-N-

prop-2-enyloxy)-benzamide;





3,4-Difluoro-2-(4-bromo-2-methyl-phenylamino)-N-(but-2-enyloxy)-benzamide;

3,4-Difluoro-2-(4-bromo-2-methyl-phenylamino)-N-(methoxy)-benzamide;

3,4-Difluoro-2-(4-bromo-2-methyl-phenylamino)-N-(ethoxy)-benzamide;

3,4-Difluoro-2-(4-bromo-2-methyl-phenylamino)-N-(cyclobutoxy)-benzamide;

3,4-Difluoro-2-(4-bromo-2-methyl-phenylamino)-N-(isopropoxy)-benzamide;

3,4-Difluoro-2-(4-bromo-2-methyl-phenylamino)-N-(2-phenoxyethoxy)-benzamide;

3,4-Difluoro-2-(4-bromo-2-methyl-phenylamino)-N-(cyclopropyl-methoxy)-benzamide;

3,4-Difluoro-2-(4-bromo-2-methyl-phenylamino)-N-(n-propoxy)-benzamide;

3,4-Difluoro-2-(4-bromo-2-methyl-phenylamino)-N-(1-methyl-prop-2-ynyloxy)-benzamide;

3,4-Difluoro-2-(4-bromo-2-methyl-phenylamino)-N-(3-(3-fluorophenyl)-prop-2-ynyloxy)-benzamide;

3,4-Difluoro-2-(4-bromo-2-methyl-phenylamino)-N-(4,4-dimethylpent-2-ynyloxy)-benzamide;

3,4-Difluoro-2-(4-bromo-2-methyl-phenylamino)-N-(cyclopentoxy)-benzamide;

3,4,5-Trifluoro-N-hydroxy-2-(4-iodo-2-methyl-phenylamino)-benzamide;

5-Chloro-3,4-difluoro-N-hydroxy-2 (4-iodo-2-methyl-phenylamino)-benzamide;

5-Bromo-3,4-difluoro-2-(2-fluoro-4-lodo-phenylamino)-N-hydroxy-benzamide;

N-Hydroxy-2-(4-iodo-2-methyl-phenylamino)-4-nitro-benzamide;

3,4,5-Trifluoro-2-(2-fluoro-4-iodo-phehylamino)-N-hydroxybenzamide;

10

5

25

30

5

10

5-Chloro-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-Nhydroxy-benzamide; 5-Bromo-2-(2-chloro-4-iodo-phenylamino)-3,4-difluoro-Nhydroxy-benzamide; 2-(2-Fluoro-4-iodo-phenylamino)-N-hydroxy-4-nitro-benzamide; 2-(2-Chloro-4-iodo-phenylamino)-3,4,5-trifluoro-N-hydroxybenzamide: 5-Chloro-2-(2-chloro-4-iodo-phenylamino)-3,4-difluoro-Nhydroxy-benzamide; 5-Bromo-2-(2-bromo-4-iddo-phenylamino)-3,4-difluoro-Nhydroxy-benzamide; 2-(2-Chloro-4-iodo-phenylamino)-N-hydroxy-4-methylbenzamide; 2-(2-Bromo-4-iodo-phenylamino)-3,4,5-trifluoro-N-hydroxybenzamide; 2-(2-Bromo-4-iodo-phenylamino)-5-chloro-3,4-difluoro-Nhydroxy-benzamide; 2-(2-Bromo-4-iodo-phenylamino)-N-hydroxy-4-nitro-benzamide; 4-Fluoro-2-(2-fluoro-4-iodo-phenylamino)-N-hydroxy-benzamide; 3,4-Difluoro-2-(2-fluoro-4-iodo-phenylamino)-N-hydroxybenzamide; 2-(2-Chloro-4-iodo-phenylamino)-4-fluoro-N-hydroxy-benzamide; 2-(2-Chloro-4-iodo-phenylamiho)-3,4-difluoro-N-hydroxybenzamide: 2-(2-Bromo-4-iodo-phenylaminb)-4-fluoro-N-hydroxy-benzamide; 2-(2-Bromo-4-iodo-phenylamind)-3,4-difluoro-N-hydroxybenzamide: N-Cyclopropylmethoxy-3,4,5-trifluoro-2-(4-iodo-2-methylphenylamino)-benzamide; 5-Chloro-N-cyclopropylmethoxy-3\4-difluoro-2-(4-iodo-2-methylphenylamino)-benzamide;

'phenylamino)-benzamide;

5-Bromo-N-cyclopropylmethoxy-3,4-difluoro-2-(2-fluoro-4-iodo-

WO 00/35436 PCT/US99/29783

N-Cyclopropylmethoxy-2-(4-iodo-2-methyl-phenylamino)-4-nitrobenzamide;

N-Cyclopropylmethoxy-3,4,5-trifluoro-2-(2-fluoro-4-iodo-phenylamino)-benzamide;

5-Chloro-N-cyclopropylmethoxy-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-benzamide;

5-Bromo-2-(2-chloro-4-iodo-phenylamino)-N-cyclopropylmethoxy-3,4-difluoro-benzamide;

N-Cyclopropylmethoxy-2-(2-fluoro-4-iodo-phenylamino)-4-nitrobenzamide;

2-(2-Chloro-4-iodo-phenylamino)-N-cyclopropylmethoxy-3,4,5-trifluoro-benzamide;

5-Chloro-2-(2-chloro-4-iodo-phenylamino)-N-cyclopropylmethoxy-3,4-difluoro-benzamide;

5-Bromo-2-(2-bromo-4-iddo-phenylamino)-N-ethoxy-3,4-difluoro-benzamide;

2-(2-Chloro-4-iodo-phenylamino)-N-ethoxy-4-nitro-benzamide;

2-(2-Bromo-4-iodo-phenylamino)-N-cyclopropylmethoxy-

3,4,5-trifluoro-benzamide;

2-(2-Bromo-4-iodo-phenylamino)-5-chloro-N-cyclopropylmethoxy-3,4-difluoro-benzamide

2-(2-Bromo-4-iodo-phenylamino)-N-cyclopropylmethoxy-4-nitrobenzamide;

N-Cyclopropylmethoxy-4-fluoro-2-(2-fluoro-4-iodo-phenylamino)-benzamide;

N-Cyclopropylmethoxy-3,4-diffuoro-2-(2-fluoro-4-iodo-phenylamino)-benzamide;

2-(2-Chloro-4-iodo-phenylamin

)-N-cyclopropylmethoxy-4-fluoro-benzamide;

2-(2-Chloro-4-iodo-phenylamino)-N-cyclopropylmethoxy-3,4-difluoro-benzamide;

2-(2-Bromo-4-iodo-phenylamino)-N-cyclopropylmethoxy-4-fluoro-benzamide; and

10.1

10

5

15())

25

20

But B!

2-(2-Bromo-4-iodo-phenylamino)-N-cyclopropylmethoxy-3,4-difluoro-benzamide

14. The method of claim 1, comprising a MEK inhibitor having a structure selected from:

2-(2-chloro-4-iodophenylamino)-5-chloro-N-cyclopropylmethoxy -3,4-difluorobenzamide (PD 297189); 2-(4-iodophenylamino)-N-cyclopropylmethoxy-5-chloro-3,4-difluorobenzamide (PD 297190); 2-(4-iodophenylamino)-5-chloro-3,4-difluorobenzoic acid (PD 296771); 2-(2-chloro-4-iodophenylamino)-5-chloro-3,4-difluorobenzoic acid (PD 296770); 5-chloro-3,4-difluoro-2-(4-iodo-2-methylphenylamino)-benzoic acid (PD 296767); and 5-chloro-N-cyclopropylmethoxy -3,4-difluoro-2-(4-iodo-2-methylphenylamino)-benzamide (PD ______).

- 15. A method of treating or preventing arthritis in a patient in need of treatment, or suspected of developing arthritis, said method comprising the step of administering an effective antiarthritic amount of a compound selected from:
- 2-(2-Chloro-4-iodophenylamino)-N-cyclopropylmethoxy-3,4-difluorobenzamide (PD184352);
- 2-(2-Methyl-4-iodophenylamino)-N-hydroxy-4-fluorobenzamide (PD170611);
- 2-(2-Methyl-4-iodophenylamino)-N-hydroxy-3,4-difluoro-5-bromobenzamide (PD171984);
- 2-(2-Methyl-4-iodophenylamino)-N-cyclopropylmethoxy-3,4-difluoro-5-bromobenzamide (PD177168);
- 2-(2-Methyl-4-iodophenylamino)-N-cyclobutylmethoxy-3.4-difluoro-5-bromobenzamide (PI) 180841);
- 2-(2-Chloro-4-iodophenylamino)-N-cyclopropylmethoxy-
- 3,4-difluoro-5-bromobenzamide (PD 184161);
- 2-(2-Chloro-4-iodophenylamino)-N-hydroxy-3,4-difluoro-5-bromobenzamide (PD184386);

¹— 20

10

25

Ay cont

5

10

2-(2-Chloro-4-iodophenylamino)-N-cyclobutylmethoxy-

3,4-difluorobenzamide (PD 185625);

2-(2) Chloro-4-iodophenylamino)-N-hydroxy-4-fluorobenzamide

(PD 185848)

2-(2-Methyl-4-iodophenylamino)-N-hydroxy-

3,4-difluoroberzamide(PD 188563);

2-(2-Methyl-4-iodophenylamino)-N-cyclopropylmethoxy-

3,4,5-trifluorobenzamide (PD 198306); and

2-(2-Chloro\4-iodophenylamino)-N-cyclopropylmethoxy-

4-fluorobenzamide (RD 203311).

16. The method of Claim 15 wherein said compound is selected from 2-(2-chloro-4-iodophenylamino)-N-cyclopropylmethoxy-

3,4-difluorobenzamide (PD 184352), 2-(2-Methyl-4-iodophenylamino)-N-cyclopropylmethoxy-3,4,5-trifluorobenzamide (PD 198306); and

2-(2-Chloro-4-iodophenylamino)-N-cyclopropylmethoxy-

4-fluorobenzamide (PD 2033 11).

ns/

	, , , , , , , , , , , , , , , , , , ,
	propyl)-3,4-difluoro-benzamide;
	4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-pyridin-4-ylmethyl-
	benzamide;
5	4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-pyridin-4-yl-
	ethyl)-benzamide;
	2-(4-Bromo-2-methyl-phenylamino)-3,4-difluoro-N-(2-pyridin-
	4-yl-ethyl)-benzamide;
	2-(4-Bromo-2-methyl-phenylamino)-3,4-difluoro-N-(3-hydroxy-
10	propyl)-benzamide;
	2-(4-Bromo-2-methyl-phenylamino)-3,4-difluoro-N-(2-pyrrolidin-
	1-yl-ethyl)-benzamide;
	4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-phenethyl-
	benzamide;
15	2-(4-Bromo-2-methyl-phenylamino)-3,4-difluoro-N-(2-thiophen-
	2-yl-ethyl)-benzamide;
	2-(4-Bromo-2-methyl-phenylamino)-3,4-difluoro-N-pyridin-
	4-ylmethyl-benzamide;
	2-(4-Bromo-2-methyl-phenylamino)-3,4-difluoro-N-phenethyl-
20	benzamide;
	2-(4-Bromo-2-methyl-phenylamino)-3,4-difluoro-N-(2-piperidin-
	1-yl-ethyl)-benzamide;
	5-Chloro-N-{3-[4-(2-hydroxy-ethyl)-piperazin-1-yl]-propyl}-
	2-(4-iodo-2-methyl- phenylamino)- benzamide;
25	5-Fluoro-N-{3-[4-(2-hydroxy-ethyl)-piperazin-1-yl]-propyl}-
	2-(4-iodo-2-methyl- phenylamino)- benzamide;
	2-(4-Iodo-2-methyl-phenylamino)-5-nitro-N-pyridin-4-yl methyl-
	benzamide;
	5-Bromo-N-{3-[4-(2-hydroxy-ethyl)-piperazin-1-yl]-propyl}-
30	2-(4-iodo-2-methyl- phenylamino)- benzamide;
	5-Chloro-N-(2-diethylamino-ethyl)-2-(4-iodo-2-methyl-
	phenylamino)- benzamide;

2-(4-Bromo-2-methyl-phenylamino)-N-(3-dimethylamino-